Published in final edited form as:

BJOG. 2015 December ; 122(13): 1728–1738. doi:10.1111/1471-0528.13172.

The association of pre-pregnancy alcohol drinking with child neuropsychological functioning

Ulrik Schiøler Kesmodel[1,2], **Maiken Ina Siegismund Kjaersgaard**[3], **Clark H Denny**[4], **Jacquelyn Bertrand**[4], **Åshild Skogerbø**[5], **Hanne-Lise F. Eriksen**[2], **Bjørn Bay**[1,2], **Mette Underbjerg**[6], and **Erik Lykke Mortensen**[7]

[1] Department of Obstetrics and Gynaecology, Aarhus University Hospital, Aarhus, Denmark

[2] Department of Public Health, Section of Epidemiology, Aarhus University, Denmark

[3] Department of Public Health, Section of Biostatistics, Aarhus University, Denmark

[4] Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA

[5] Division of Psychiatry, University of Stavanger, Norway

[6] Children's Neurocenter at Vejlefjord Rehabilitation Center, Denmark

[7] Institute of Public Health and Center for Healthy Aging, University of Copenhagen, Denmark

Abstract

Objective—To examine the effects of pre-pregnancy alcohol drinking on child neuropsychological functioning.

Design—Prospective follow-up study.

Setting and population—154 women and their children sampled from the Danish National Birth Cohort.

Methods—Participants were sampled based on maternal alcohol consumption before pregnancy. At 5 years of age, the children were tested with the Wechsler Preschool and Primary Scale of Intelligence-Revised, the Test of Everyday Attention for Children at Five (TEACh-5), and the

Correspondence to Ulrik Schiøler Kesmodel, Department of Obstetrics and Gynaecology, Aarhus University Hospital, 8200 Aarhus N, Denmark. ulrikesm@rm.dk.

Contributions

Ulrik Schiøler Kesmodel, Jacquelyn Bertrand, and Erik Lykke Mortensen contributed to the conception and design of the study. Ulrik Schiøler Kesmodel, Jacquelyn Bertrand, Åshild Skogerbø, Hanne-Lise F Eriksen, Mette Underbjerg ,and Erik Lykke Mortensen contributed with acquisition of data. Maiken IS Kjaersgaard analysed the data. Ulrik Schiøler Kesmodel, Maiken IS Kjaersgaard, Clark H Denny, Jacquelyn Bertrand, Åshild Skogerbø, Hanne-Lise F Eriksen, Bjørn Bay, Mette Underbjerg and Erik Lykke Mortensen contributed with interpretation of data, reviewed the first and subsequent drafts of the article and revised it critically for intellectual content, and approved the final version before submission. Ulrik Schiøler Kesmodel drafted the article and revised it before submission.

Disclaimer: The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflicts of interest: none

Ethics

The study was approved by the DNBC Board of Directors, the DNBC Steering committee, the regional Ethics Committee, the Danish Data Protection Agency, and the Institutional Review Board at the Centers for Disease Control and Prevention. Signed informed consent was obtained for the LDPS.

Movement Assessment Battery for Children (MABC).The Behaviour Rating Inventory of Executive Function (BRIEF) were completed by the mothers and a preschool teacher. Parental education, maternal IQ, prenatal maternal smoking, child's age at testing, child's sex, and alcohol intake during pregnancy were considered potential confounders.

Main outcome measures—Performance on the Wechsler Preschool and Primary Scale of Intelligence-Revised, the TEACh-5, the MABC, and the BRIEF.

Results—Intake of 15-21 drinks/week on average prior to pregnancy was not associated with any of the outcomes, but intake of ≥22 drinks/week on average was associated with a significantly lower adjusted mean full scale IQ and lower adjusted means in overall attention and sustained attention score, but not in selective attention score or any of the BRIEF index scores or MABC scores.

Conclusions—Intake of ≥22 drinks/week before pregnancy was associated with lower mean full scale IQ, overall attention and sustained attention. Assessment of pre-pregnancy drinking provides additional information regarding potential prenatal alcohol exposure and its implications for child neurodevelopment.

Keywords

Pregnancy; alcohol drinking; neurodevelopmental effects; intelligence; attention; executive function; motor function

Introduction

Intake of alcohol during pregnancy can be harmful for the developing fetus and cause miscarriage,[1] preterm birth, growth retardation,[2] and malformations.[3] Neurodevelopmentally, it can adversely affect several cognitive domains.[4-6] These findings have come primarily from studies of drinking at moderate to heavy levels, involving daily or chronic drinking.

With respect to lower levels of alcohol use during pregnancy, findings are more complex. A recent, large cohort study showed no statistically significant differences between children whose mothers consumed 1-8 drinks per week and those who abstained with respect to intelligence,[7;8] attention,[8;9] executive function,[8;10] behaviour[8;11] or motor function.[12] Further, a recent meta-analysis assessed the association between average weekly alcohol intake of >0 - ≤6 drinks per week and neuropsychological development of the child[13] and revealed no significant associations between any of the exposure categories and the included neuropsychological outcomes (i.e., visual- motor function, attention, cognition, behavior, development, or language skills). However, when restricting analyses to studies of high quality only, a detrimental association between average weekly intake of 3- ≤6 drinks and child behavior was observed as was a small, statistically significant, beneficial association between average weekly intake of >0 - ≤6 drinks and child cognition.

An important aspect for these studies is the timing and pattern of alcohol exposure assessment. In some studies, alcohol binge drinking has been assessed week by week in early pregnancy before and after the assumed time of conception, [7;8] thereby taking into

account timing of exposure. However, for average alcohol intake, such detailed information on exposure has not been published.

Studies comparing pre-pregnancy and pregnancy alcohol consumption have shown that approximately half of all women stop drinking once pregnancy is recognized.[14;15] Of the women who do not completely stop drinking during pregnancy, the majority reduce their alcohol consumption to much lower weekly levels. It is likely that especially women with unplanned pregnancies may have continued drinking at pre-pregnancy levels during the very early weeks of pregnancy before pregnancy recognition.

Alcohol use problems prior to pregnancy as measured by TWEAK[16] (a validated instrument used to screen for risk drinking behaviour by asking indirect questions about e.g. Tolerance, Worries in the family, use of an Eyeopener, etc.) has been associated with adverse obstetrical outcomes, even in the absence of in-pregnancy alcohol use.[17] However, the association between peri- or pre-conceptional alcohol use and later neuropsychological development of the child has not been investigated. We used data from the Lifestyle During Pregnancy Study (LDPS)[8;18] to assess the association between high average maternal reported pre-pregnancy alcohol intake and intelligence, attention, executive function and motor function of the child resulting from the subsequent pregnancy.

Methods

Participants

The LDPS has been described in detail elsewhere, including the oversampling of women with high alcohol intake.[8;18] Briefly, participants were drawn from the Danish National Birth Cohort (DNBC), a prospective cohort study of 101,042 women and their children.[19] Women in the DNBC were recruited from 1997-2003, at their first antenatal visit at a general practitioner (routinely the first contact to a healthcare practitioner for a pregnant woman in Denmark). Participating women represent 60% of those invited and approximately 30% of all pregnant women in Denmark in the enrollment period.

Only women explicitly sampled on the basis of alcohol intake before pregnancy were eligible for the present analysis (N=289). Of these eligible participants, 154 mother-child pairs consented/assented and were tested. [8;18] The children were 60-64 months of age (mean= 5.2 years, 10/90 percentile = 5.1-5.3) at the time of testing. Fifty one percent of the children were boys.

Exclusion criteria for the LDPS were mother's or child's inability to speak Danish, impaired hearing or vision of the child to the extent that it was likely to affect the child's test performance, child from a multiple pregnancy, and congenital disorders likely to cause mental retardation (e.g. Down syndrome).

Measures

Exposure variables—We obtained information on alcohol consumption before and during the index pregnancy from the first DNBC interview administered at a median 17 weeks of gestation (10/90 percentile 12–24 weeks) for those participating in this follow up

study. Questions assessed the average number of drinks per week of beer, wine, and spirits that the pregnant woman consumed before the index pregnancy. The definition of a drink was 12 grams of pure alcohol (following the definition from the Danish Health and Medicines Authority). Women were sampled on the basis of alcohol intake before pregnancy: If they reported being abstainers before and during pregnancy (reference group), or reported consuming an average of ≥15 drinks per week before pregnancy (exposed group), which is more than the maximum recommended level for non-pregnant women by the Danish Health and Medicines Authority at the time of the study (maximum of 14 drinks per week).[20] Subsequently, maternal average weekly alcohol intake before pregnancy was categorized into three groups (0, 15-21, ≥22 drinks/week). Intake above the maximum recommended level was chosen to achieve maximum contrast between the exposed and unexposed groups. With respect to the categorization of the 15+ group, we chose two categories based on the small numbers, and used the 15-21 (corresponding to >2 -3 drinks/day) and ≥22 (>3 drinks/day) categories, because this would be comparable to other studies using daily intake as their unit.

Outcome variables—The LDPS included a comprehensive neuropsychological assessment of the children at age 5, which has been described in detail elsewhere.[8;18] Sampled mothers were invited by letter to participate in the study 3-10 weeks (mean=5.8) before their child's fifth birthday. A self-administered questionnaire for the parents regarding the child's general postnatal health and development as well as maternal and paternal postnatal lifestyle was mailed to the participants.

When the child was between 60 and 64 month old, a 3-hour assessment was carried out in one of four test sites, ensuring that assessment took place within a manageable travel distance for all mothers and children.

Analyses in this paper assessed primary outcomes of intelligence, attention, executive and motor function using a standard intelligence test, a project-developed test of attention validated on a separate group of Danish pre-schoolers, a standard rating scale of executive functioning for pre-schoolers, and a test of motor function (performed only between September 2003 and February 2006).

Intelligence: We assessed intelligence with the Wechsler Primary and Preschool Scales of Intelligence-Revised (WPPSI-R), one of the most widely used, standardized tests of intelligence for three to seven year old children.[21] It consists of five verbal subtests and five performance (non-verbal) subtests from which verbal (VIQ), performance (PIQ), and full scale (FSIQ) IQs are derived. We used a short form including three verbal (Arithmetic, Information and Vocabulary) and three performance subtests (Block Design, Geometric Design and Object Assembly) in order to reduce the length of the test session. Standard procedures were used to prorate IQs from the shortened forms of the tests. No Danish WPPSI-R norms were available at the time of the study, and therefore Swedish norms were used to derive scaled scores and IQs.

Attention: Attention was measured by the Test of Everyday Attention for Children at Five (TEACh-5).[9] Detailed description of development of the TEACh-5, validation and its

psychometric properties are provided elsewhere.[22] For the present analyses we used selective attention and sustained attention. Selective attention was composed of a non-verbal cancellation task and an auditory task of listening for a specific target among distracters. Sustained attention consisted of an auditory task of counting the number of times a target sound was produced at various rates of presentation and a visual motor task of drawing a line as slowly as possible.

The number correct and the log-transformed scores (auditory target identification and drawing a line) were first standardized to a mean of 0 and a SD of 1 based on the full LDPS sample. The mean of the four standardized subscores were subsequently calculated and re-standardized to a mean of 0 and a SD of 1 for use in the statistical analyses as a composite measure of overall attention.

Executive Function: The Behavior Rating Inventory of Executive Function (BRIEF) is an 86 item questionnaire that assesses executive function behaviors in the home as rated by the mother and in the day care environment as rated by staff.[23] Only data on the three standardized index scores: Behavioral Regulation Index (BRI), Metacognition Index (MI) and Global Executive Composite (GEC) are presented in this paper.

A translated version of the BRIEF was used (Hogrefe Psychological Publishers) with minor adjustments for Danish preschool children. We constructed our own Danish norms based on the full LDPS sample, because no Danish BRIEF norms were available at the time of the study. A normalizing *T*-score transformation for the observed BRIEF scores was computed, with higher scores indicating more difficulties.

Motor Function: Motor function was assessed by the Movement Assessment Battery for Children (MABC),[24] a widely used standardized instrument for the detection of mild to moderate motor difficulties in children. The performance test requires the child to perform a series of eight standardized motor tasks covering gross and fine motor function and static and dynamic balance. Every task is scored from 0-5 according to the speed and number of correctly executed components of each task and thus, the total scores on the performance test is 0-40, with lower scores indicating a better performance. The total motor impairment score (TIS) can be interpreted by using percentile norm tables for the specific age group. The quantitative part of the MABC has been shown to have high inter-rater and test-retest reliability[25;26] and moderate concurrent validity .[25]

Covariates—From the prenatal interview, the following covariates were included: Maternal average weekly alcohol intake during pregnancy at the time of the interview and maternal alcohol binge drinking in early pregnancy (≥5 drinks on a single occasion before the time of the first DNBC interview); prenatal maternal smoking (yes/no). From the 5-year follow-up, the following variables were included: length of parental education in years (the average educational length for the two parents or length of maternal education if information on the father was unavailable, analyzed as a continuous measure).

Maternal IQ was assessed using two verbal subtests (Information and Vocabulary) from the Wechsler Adult Intelligence Scale[27] (WAIS) and the Raven's Standard Progressive

Matrices.[28] We standardized the raw scores based on the results from the full sample and weighted them equally in a combined score, re-standardized to an IQ scale with a mean of 100 and an SD of 15.

Maternal age was obtained directly from the unique Danish personal identification number, as was sex of child and age of child at testing.

Statistical analysis

Associations between pre-pregnancy maternal alcohol exposure categories (0, 15-21, ≥22) and the continuous measures of FSIQ, VIQ, PIQ, overall attention, selective attention, sustained attention, BRIEF BRI, MI and GEC, and the MABC outcome scores were estimated using multiple linear regression. Parental education, maternal IQ, maternal smoking during pregnancy, the child's age at testing, the child's sex, and prenatal maternal average weekly alcohol intake were considered potential confounders. In sub-analyses, maternal binge drinking during early pregnancy was used instead of average weekly alcohol intake. Because of the overall sample size, to maximize variance for variables of interest, the number of potential confounders selected for the analyses was restricted to those most relevant for those neurodevelopmental constructs.

Missing values were imputed based on the following two strategies: A dedicated model for imputations, for which variables were modeled from other variables considered to be most predictive (specific equations available upon request), and a black-box strategy for which all variables were used to predict missing values. The main conclusions were essentially unaffected by imputation strategy and point estimates of the exposure parameters did not differ by more than 0.6% relative to standard error. All conclusions were maintained when complete case analysis was conducted. The results of the dedicated imputation strategy are reported. All imputations were implemented with the -ice- add-on command,[29] and the built-in -mi estimate- command of Stata 11.

All analyses were weighted by sampling fractions with robust variance estimation to account for the complex stratified sampling design, and all statistical tests were two-sided and declared significant at 5% level. All estimates include 95% confidence intervals. No adjustment was made for multiple comparisons, as most methods tend to yield conservative estimates, which in the case of risk of adverse outcomes would be to err in the wrong direction.

The study was approved by the DNBC Board of Directors, the DNBC Steering committee, the regional Ethics Committee, the Danish Data Protection Agency, and the Institutional Review Board at the Centers for Disease Control and Prevention. Signed informed consent was obtained for the LDPS.

Results

No systematic differences were observed between the participating and non-participating mother and child pairs with respect to observed characteristics (Table 1).

Table 2 shows the descriptive characteristics of the participants across average number of drinks per week before pregnancy. Based on reported average drinking only, across exposure levels, 62 women (40%) reported drinking pre-pregnancy and continued to drink during pregnancy, 23 (15%) reported drinking pre-pregnancy but did not report drinking during pregnancy, and 69 (44%) drank neither before nor during pregnancy. Women who reported being an abstainer before and during pregnancy were more likely to have significantly lower maternal IQ, lower maternal education, higher parity, and be younger and a non-smoker, while a suboptimal home-environment index was increasingly more common among those with increasing pre-pregnancy alcohol intake. There were no significant differences by alcohol intake and other family or child characteristics (Table 2).

Regarding child outcomes, average intake of 15-21 drinks per week before pregnancy was not associated with IQ, attention, executive function or motor function (Tables 3 – 6).

Intake of ≥22 drinks/week on average before pregnancy was associated with a significantly lower adjusted mean FSIQ with a difference of −6.33 IQ points (95% CI: −12.56; −0.10) compared to abstainers. The differences in VIQ and PIQ were of a comparable magnitude, although not significantly different from the children of mothers who did not drink prior to pregnancy (Table 3). When adjusting for binge drinking in early pregnancy instead of average alcohol intake during pregnancy, larger mean differences appeared for the ≥22 drinks/week-group: −10.29 (95% CI: −16.98; −3.61) for FSIQ, −5.69 (95% CI: −10.74; −0.65) for VIQ, and −12.98 (95% CI: −23.65; −2.30) for PIQ.

An intake of ≥22 drinks/week on average prior to pregnancy also was associated with significantly lower adjusted means in overall attention score and sustained attention score, but not in selective attention score (Table 4). Adjustment for binge drinking in early pregnancy instead of average alcohol intake during pregnancy did not change the magnitude or the significance of the results (data not shown).

We found no significant association between alcohol intake prior to pregnancy and any of the BRIEF index scores (Table 5) or MABC scores (Table 6), including subscales of MABC scores (data not shown). Adjusting for binge drinking during early pregnancy instead of average alcohol intake during pregnancy did not change these conclusions (data not shown).

P-value for the hypothesis of no difference in adjusted scores across all levels of average alcohol intake before pregnancy were significant for FIQ and VIQ scores (Table 3), overall and sustained attention scores (Table 4) and MABC scores (Table 6). However, there was a systematic, negative trend across all the alcohol categories only for the adjusted attention scores (Table 4), whereas for IQ and motor function, the adjusted scores for the 15-21 drinks/week groups showed at positive (albeit insignificant) association (Tables 3 and 6).

Discussion

Main findings

We found that intake of ≥22 drinks/week on average prior to pregnancy was associated with a significantly lower adjusted mean FSIQ, and that the differences in mean VIQ and PIQ

were of a comparable magnitude. Intake of ≥22 drinks/week also was associated with significantly lower adjusted means in overall attention score and sustained attention score, but not selective attention score, executive function scores, or MABC scores. Intake of 15-21 drinks per week on average before pregnancy was not associated with IQ, attention, executive function, or motor function.

Strengths & limitations

The risk of selection bias in this study is small. As reported elsewhere, there were no significant differences between the participating and non-participating LDPS sample.[7] Although the participants in the DNBC were likely to be healthier than other women, this causes only little if any bias in within DNBC analyses.[30] Second, the neurodevelopmental assessment was based on some of the most widely used, validated measures of intelligence and executive function for children. In addition, trained psychologists, with no knowledge of the reported maternal alcohol intake, performed the assessments. Third, the participants represented a homogenous middle class population with respect to health, lifestyle and socioeconomic status, thereby reducing the risk of confounding by socio-economic factors.

Interpretation - finding in light of other evidence

Alcohol risky drinking prior to pregnancy has been associated with low Apgar score, pre-labor rupture of membranes, reduced birth weight, and gestational age.[17] Even among women who reported risky drinking before pregnancy but no alcohol intake during pregnancy, increased risk of pre-labor rupture of membranes and reduced birth weight has been reported.[17]

We have previously described for the LDPS that intake of 1-8 drinks/week on average during pregnancy and binge drinking in early pregnancy were not systematically associated with child IQ,[7;31] attention (including selective and sustained attention),[9] executive function,[10] motor function[12;32] or behavior.[11] This raises the issue of how to explain that high alcohol intake before pregnancy (≥22 drinks/week on average) and peri-conceptionally appears to substantially reduce IQ and attention scores, while alcohol intake during pregnancy at the levels reported by the same women (table 2) does not.

First, in the present study pre-pregnancy drinking represented heavier levels of drinking, not the low to moderate levels of most women in previous LDPS analyses. Because women may have been reporting alcohol consumption levels prior to pregnancy recognition rather than prior to conception,[14] significant prenatal exposure to alcohol by the fetus may have still occurred during very early gestation.[6] Further, 40% women reported that they continued to drink, and these women would be drinking at the higher levels involving potentially significant exposure prior to pregnancy recognition. Thus, assessment of pre-pregnancy may be more accurate in determining prenatal exposure, or at least have added clinical utility.

Underreporting of alcohol intake during pregnancy is likely, but this would explain the described associations only if the vast majority of women with a high intake of ≥22 drinks per week on average before pregnancy are indeed at high risk, and these women completely deny any alcohol intake during pregnancy, thereby reducing the potential contrast between non-drinkers and weekly drinkers during pregnancy. However, in this study 63.2% of the

women reporting intake of ≥22 drinks per week on average before pregnancy reported intake of 1-8 drinks per week on average during pregnancy.

All the women in the two alcohol drinking groups in this study reported a reduction in alcohol intake by the early second trimester, no one reporting intake of more than 8 drinks per week on average, most of them a maximum of 4 drinks per week (Table 2). If validly reported, such a reduction in drinking should have reduced exposure to below estimated risk levels during pregnancy as regards to neurodevelopmental outcomes. Thus another possibility is that by restricting the number of covariates, the present analysis is left with the possibility of unadjusted (residual) confounding. In previous analyses of the LDPS, the larger sample allowed us to adjust for a larger number of pre- and postnatal variables including for example parental education, maternal IQ, prenatal maternal smoking and average weekly alcohol intake and/or binge drinking, maternal age, parity, prenatal and postnatal marital status, postnatal parental smoking, maternal pre-pregnancy BMI, the child's sex and age, health status, hearing and vision on the day of testing, family/home environment, and tester.[7-10;31;32] Even so, we included what appears to be the most important confounders: maternal IQ and parental education.[33]

Alternatively, alcohol – and possibly other toxic agents –most likely induce epigenetic changes in the gametes before or around the time of conception.[34] Thus, the differentiating and imprinting process occurs during maturation in the developing spermatogonia and the oogonia, but for both, the process is accomplished before fertilization.[35] This, however, remains speculative at this point.

Another question is: Why is the association with IQ stronger when adjusting for binge drinking during early pregnancy than when adjusting for average weekly alcohol intake? Many of the women reporting ≥15 drinks per week on average before pregnancy also reported binge drinking episodes. In fact, in our study, there were more binge drinkers among participants than among non-participants (Table 1). In the LDPS, we have previously shown that high average alcohol intake of ≥9 drinks/week was marginally associated with low IQ[7] while binge drinking in early pregnancy was not.[31] It may be that average weekly alcohol intake during pregnancy is simply a stronger confounder than binge drinking during pregnancy, and therefore estimates adjusted for binge drinking leave more room for residual confounding than estimates adjusted for average weekly alcohol intake. Alternatively, information on binge drinking may be more precise and therefore more valid, leaving less room for information bias. However, both types of information were collected with validated instruments, reducing the risk of potential misclassification.[36;37]

Conclusion

In summary, we observed that intake of ≥22 drinks/week on average before pregnancy was associated with lower mean full scale IQ, overall attention and sustained attention, but not with selective attention, executive function and motor function. Thus, assessment of pre-pregnancy (or peri-conceptional) drinking provides additional information regarding potential prenatal alcohol exposure and its implications for child neurodevelopment. In the absence of a comparable association with average alcohol intake and binge drinking during early pregnancy, the described association may be due to uncontrolled confounding or

misreporting consumption during pregnancy but prior to pregnancy recognition, although other explanations such as epigenetic changes cannot be ruled out.

However, to avoid any risk for women who may become pregnant (i.e. trying to become pregnant or not consistently using an effective method of contraception), the current advice in most countries is to abstain from consuming alcohol,[38;39] especially since significant exposure may occur prior to pregnancy recognition. Based on studies of within pregnancy drinking, however, this advice may need to be refined, and clearly additional data, both before pregnancy recognition and during pregnancy, are needed to clarify messages and recommendations to women. Future studies may want to focus on measuring peri-conceptional drinking, distinguishing between pre- and postconceptional drinking as well as drinking before and after pregnancy recognition.

Acknowledgement

This study was primarily supported by the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA. Additional support was obtained from the Danish National Board of Health, the Lundbeck Foundation, Ludvig & Sara Elsass' Foundation, the Augustinus Foundation, and Aase & Ejnar Danielsen's Foundation.

The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this Foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation and the Health Foundation.

The authors would like to thank all the participants for their time and efforts.

Funding

This study was primarily supported by the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA. Additional support was obtained from The Danish National Board of Health, the Lundbeck Foundation, Ludvig & Sara Elsass' Foundation, the Augustinus Foundation, and Aase & Ejnar Danielsen's Foundation.

References

1. Windham GC, Fenster L, Swan SH. Moderate maternal and paternal alcohol consumption and the risk of spontaneous abortion. Epidemiology. 1992; 3(4):364–370. [PubMed: 1637900]
2. Patra J, Bakkr R, Irving H, Jaddoe VWV, Malini S, Rehm J. Dose-repsonse relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA) - a systematic review and meta-analyses. BJOG. 2011; 118(12): 1411–21. [PubMed: 21729235]
3. Mills JL, Graubard BI. Is moderate drinking during pregnancy associated with an increased risk for malformations? Pediatrics. 1987; 80(3):309–14. [PubMed: 3627880]
4. Coles CD, Platzman KA, Lynch ME, Freides D. Auditory and visual sustained attention in adolescents prenatally exposed to alcohol. Alcohol Clin Exp Res. 2002; 26(2):263–71. [PubMed: 11964567]
5. Noland JS, Singer LT, Arendt RE, Minnes S, Short EJ, Bearer CF. Executive functioning in preschool-age children prenatally exposed to alcohol, cocaine, and marijuana. Alcohol Clin Exp Res. 2003; 27(4):647–56. [PubMed: 12711927]
6. Riley EP, Infante MA, Warren KR. Fetal alcohol spectrum disorders: an overview. Neuropsychol Rev. 2011; 21(2):73–80. [PubMed: 21499711]
7. Eriksen H-LF, Mortensen EL, Kilburn TR, Underbjerg M, Bertrand J, Støvring H, et al. The effects of low to moderate alcohol exposure in early pregnancy on IQ in 5-year-old children. BJOG. 2012; 119(10):1191–1200. [PubMed: 22712749]

8. Kesmodel US, Bertrand J, Støvring H, Skarpness B, Denny C, Mortensen EL, et al. The effect of different alcohol drinking patterns in early to mid-pregnancy on child's intelligence, attention and executive function. BJOG. 2012; 119(10):1180–1190. [PubMed: 22712700]
9. Underbjerg M, Kesmodel US, Landrø NI, Bakketeig LS, Grove J, Wimberley T, et al. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on selective and sustained attention in five-year-old children. BJOG. 2012; 119(10):1211–1221. [PubMed: 22712829]
10. Skogerbø Å , Kesmodel US, Wimberley T, Støvring H, Bertrand J, Landrø NI, et al. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on executive function in five-year-old children. BJOG. 2012; 119(10):1201–1210. [PubMed: 22712874]
11. Skogerbø Å , Kesmodel US, Denny CH, Kjaersgaard MIS, Wimberley T, Landrø NI, et al. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on behaviour in 5-year-old children: a prospective cohort stuidy on 1628 children. BJOG. 2013
12. Bay B, Støvring H, Wimberley T, Denny C, Mortensen EL, Eriksen H-LF, et al. Low to Moderate Alcohol Intake During Pregnancy and Risk of Psychomotor Deficits. Alcohol Clin Exp Res. 2012; 36(5):807–814. [PubMed: 21995343]
13. Flak AL, Su S, Bertrand J, Denny CH, Kesmodel US, Cogswell ME. The association between mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. Alcohol Clin Exp Res. 2014; 38(1):214–26. [PubMed: 23905882]
14. Floyd RL, Decoufle P, Hungerford DW. Alcohol use prior to pregnancy recognition. Am J Prev Med. 1999; 17(2):101–7. [PubMed: 10490051]
15. Kesmodel U, Kesmodel PS, Larsen A, Secher NJ. Use of alcohol and illicit drugs among pregnant Danish women, 1998. Scand J Public Health. 2003; 31(1):5–11. [PubMed: 12623518]
16. Russell M, Martier SS, Sokol RJ, Mudar P, Bottoms S, Jacobson S, et al. Screening for pregnancy risk-drinking. Alcohol Clin Exp Res. 1994; 18(5):1156–61. [PubMed: 7847599]
17. Flynn HA, Berman D, Marcus SM. The relationsship between obstetrical outcomes and alcohol use in the year prior to pregnancy. J Psychosom Obstet Gynaecol. 2009; 30(4):255–61. [PubMed: 19922398]
18. Kesmodel US, Underbjerg M, Kilburn TR, Bakketeig LS, Mortensen EL, Landrø NI, et al. Lifestyle during pregnancy: Neurodevelopmental effects at 5 years of age. The design and implementation of a prospective follow-up study. Scand J Public Health. 2010; 38(2):208–219. [PubMed: 20064917]
19. Olsen J, Melbye M, Olsen SF, Sorensen TI, Aaby P, Andersen AM, et al. The Danish National Birth Cohort--its background, structure and aim. Scand J Public Health. 2001; 29(4):300–307. [PubMed: 11775787]
20. Gronbaek MN, Iversen L, Olsen J, Becker PU, Hardt F, Sorensen TI. [Sensible drinking limits] Genstandsgrænser. Ugeskr Laeger. 1997; 159(40):5939–45. [PubMed: 9381567]
21. Wechsler, D. Manual for the Wechsler Preschool and Primary Scale of Intelligence - Revised. The Psychological Corporation; Sidcup, Kent: 1990. UK edition ed
22. Underbjerg M, George M, Thorsen P, Kesmodel US, Mortensen EL, Manly T. Separable sustained and selective attention factors are apparent by 5-years. PLoS One. 2013; 8(12):e82843. [PubMed: 24376591]
23. Gioia, GA.; Isquith, PK.; Guy, SC.; Kenworthy, L. Behavior Rating Inventory of Executive Function: Professional Manual. Psychological Assesment Resources, Inc; Lutz, Florida: 2000.
24. Henderson, S.; Sugden, D. Movement Assessment Battery for Children. 2. Dansk Psykologisk Forlag; København: 2001.
25. Croce RV, Horvat M, McCarthy E. Reliability and concurrent validity of the movement assessment battery for children. Percept Mot Skills. 2001; 93:275–280. [PubMed: 11693695]
26. Smits-Engelsman BCM, Fiers MJ, Henderson SE, Henderson L. Interrater reliability of the movement assessment battery for children. Phys Ther. 2008; 88:286–94. [PubMed: 18073266]
27. Wechsler, D. Manual for the Wechsler Adult Intelligence Scale. The Psychological Corporation; New York: 1955.
28. Raven, J.; Raven, J.; Court, J. Manual for Raven's Progressive Matrices and Vocabulary Scales. Oxford Psychologists Press, Ltd.; Oxford: 1998.

29. Royston P. Multiple imputation of missing values: Further update of ice, with an emphasis on categorical variables. Stata Journal. 2009; 9(3):466–77.

30. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? Epidemiology. 2006; 17:413–18. [PubMed: 16755269]

31. Kesmodel US, Eriksen H-LF, Underbjerg M, Kilburn TR, Støvring H, Wimberley T, et al. The effect of alcohol binge drinking in early pregnancy on child's general intelligence. BJOG. 2012; 119(10):1222–31. [PubMed: 22712770]

32. Kesmodel US, Bay B, Wimberley T, Eriksen H-LF, Mortensen EL. Does Binge Drinking During Early Pregnancy Increase the Risk of Psychomotor Deficits? Alcohol Clin Exp Res. 2013; 37(7): 1204–12. [PubMed: 23414523]

33. Eriksen H-LF, Kesmodel US, Underbjerg M, Kilburn TR, Bertrand J, Mortensen EL. Predictors of intelligence at the age of 5: family, pregnancy and birth characteristics, postnatal influences, and postnatal growth. PLoS One. 2013; 8(11):e79200. [PubMed: 24236109]

34. Lidegaard Ø , Pinborg A, Andersen AN. Imprinting disorders after assisted reproductive technologies. Curr Opin Obstet Gynecol. 2006; 18(3):293–96. [PubMed: 16735829]

35. Gosden R, Trasler J, Lucifero D, Faddy M. Rare congenital disorders, imprinted genes, and assisted reproductive technology. Lancet. 2003; 361(9373):1975–77. [PubMed: 12801753]

36. Kesmodel U, Olsen SF. Self-reported alcohol intake in pregnancy: comparison between four methods. J Epidemiol Community Health. 2001; 55(10):738–45. [PubMed: 11553658]

37. Kesmodel U. Binge drinking in pregnancy - frequency and methodology. Am J Epidemiol. 2001; 154(8):777–82. [PubMed: 11590091]

38. Danish Health and Medicines Authority. 2007. www.sst.dk/publ/Publ2007/CFF/Alkohol_graviditet/Alk_grav.pdf

39. National Health and Medical Research Counsil. Australian guidelines to reduce health riska from drinking alcohol. Commonwealth of Australia; Canberra: 2009.

Table 1

Maternal and child characteristics of participants and non-participants, Denmark 2003-2008.

	Eligible Participants tested	Questionnaire only	Non-participants	Total
Number of participants	154	11	124	289
Sampling fraction *(Median, 10th/90th percentile)*	13.8 (1.4/14.9)	1.4 (1.4/14.9)	1.4 (1.4/14.9)	11.7 (1.4/14.9)
Timing of interview, *gestational week (median, 10th/90th percentile)*	17.0 (12.0/24.0)	16.0 (12.0/21.0)	17.0 (13.0/23.0)	17.0 (13.0/24.0)
Maternal characteristics				
Age, years *(Mean ± SD)*	29.9 ± 4.6	27.0 ± 3.0	30.0 ± 5.4	29.8 ± 4.9
Prenatal marital status *Single (%)*	4.5	9.1	6.5	5.5
Parity				
0(%)	59.7	63.6	48.4	55.0
1(%)	31.2	27.3	30.6	30.8
≥2(%)	9.1	9.1	21.0	14.2
Maternal pre-pregnancy BMI, kg/m^2 *(Median, 10/90 pctile)*	22.8 (19.4/29.1)	21.5 (18.0/27.5)	23.8 (20.0/30.0)	23.2 (19.6/29.6)
Smoking in pregnancy *Smokers (%)*	33.8	36.4	43.5	38.1
Binge drinkers during early pregnancy (%)[1]	31.8	9.1	22.6	27.0
Child characteristics				
Gender *Male (%)*	50.6	27.3	48.4	48.8
Birth weight, grams *(Mean ± SD)*	3620.2 ± 510.2	3167.2 ± 434.3	3647.4 ± 564.4	3614.6 ± 537.7
Gestational age at birth, days *(Median, 10/90 pctile)*	281.5 (268.0/294.0)	282.0 (271.0/285.0)	283.5 (269.0/294.0)	282.0 (268.0/294.0)

[1] Defined as intake of 5 drinks or more at one occasion.

Table 2

Sample characteristics[1] across average number of drinks per week before pregnancy, Denmark 2003-2008.

	Average number of drinks per week prior to pregnancy				
	0	**15-21**	**≥22**[2]	**Total**	**p-values**[3]
Number of participants	69	66	19	154	
Sampling fraction *(Median, 10th/90th percentile)*	1.4 (1.4/1.4)	14.3 (13.6/14.9)	14.3 (13.9/14.9)	13.8 (1.4/14.9)	
Timing of interview, *gestational week (median, 10th/90th percentile)*	16 (12/25)	17 (13/24)	18 (12/26)	17 (12/24)	0.44
Family characteristics					
Maternal age, years *(Mean ± SD)*	28.9 ± 3.7	31.0 ± 4.8	29.4 ± 5.8	29.9 ± 4.6	0.02
Parity					<0.01
0(%)	33.3	78.8	89.5	59.7	
1(%)	50.7	18.2	5.3	31.2	
≥2(%)	15.9	3.0	5.3	9.1	
Maternal pre-pregnancy BMI, kg/m^2 *(Median, 10/90 percentile)*	23.2 (20.3/31.1)	22.6 (19.3/27.7)	22.4 (18.0/26.7)	22.8 (19.4/29.1)	0.08
Maternal marital status[4] *Single (%)*	13.0	16.7	21.1	15.6	0.68
Parental education, years *(Median, 10/90 pctile)*	12.0 (10.5/14.5)	14.0 (11.0/16.5)	14.0 (10.0/17.0)	13.0 (10.5/16.0)	<0.01
Family/home index *Suboptimal*[5] *(%)*	17.4	22.7	63.2	25.3	<0.01
Maternal IQ *(Mean ± SD)*	96.5 ± 13.6	103.0 ± 14.8	101.2 ± 19.9	99.9 ± 15.2	0.03
Maternal prenatal smoking *Smokers (%)*	23.2	42.4	42.1	33.8	0.04
Postnatal parental smoking *Smokers (%)*	30.4	36.4	52.6	35.7	0.18
Average alcohol consumption during pregnancy					
0 drinks/week (%)	100.0	24.2	36.8	59.7	
1-4 drinks/week (%)	0	71.2	57.9	37.7	
5-8 drinks/week (%)	0	4.5	5.3	2.6	
Binge drinkers during early pregnancy (%)[6]	0	57.6	57.9	31.8	0.91
Child characteristics					
Gender					0.67
Male (%)	52.2	51.5	42.1	50.6	
Age at testing in years *(Median, 10/90 percentile)*	5.2 (5.1/5.3)	5.2 (5.1/5.3)	5.3 (5.1/5.3)	5.2 (5.1/5.3)	0.28
Birth weight, grams *(Mean ± SD)*	3658.1 ± 511.8	3664.6 ± 448.8	3330.7 ± 628.1	3620.2 ± 510.2	0.07

	Average number of drinks per week prior to pregnancy				
	0	**15-21**	**≥22**[2]	**Total**	**p-values**[3]
Gestational age, days *(Median, 10/90 pctile)*	280 (263/293)	283.5 (273/294)	281 (241/298)	281.5 268/294)	0.07
Health status					0.21
Condition/medicine[7] *(%)*	2.9	0.0	10.5	2.6	
No sports (%)	25.0	38.1	46.7	33.1	0.16
Hearing abilities *Normal (%)*	89.9	98.5	94.7	94.2	0.17
Vision abilities *Normal (%)*	94.2	93.9	94.7	94.2	0.97

[1] Based on unweighted data. P-values based on weighted analyses.

[2] Range: 22.0-41.5 drinks per week.

[3] P-values for differences across all alcohol consumption groups based on weighted analyses.

[4] Single if single either in pregnancy or at follow-up (60-64 months postpartum).

[5] Defined as a score on at least 2 of the following items: single parent household; changes in care giving; day care >8 hrs/day before age 3; 14+ days away from home; irregular breakfast meals; maternal depression; parental alcohol use above the maximum recommended level at the time by the Danish Health and Medicines Authority of 14 drinks per week for women and 21 drinks per week for men..

[6] ≥5 drinks on one occasion.

[7] Medical conditions or regular medications that may influence test performance.

Table 3

Associations between maternal alcohol intake before pregnancy and offspring mean WPPSI-R[1] full scale IQ, verbal IQ and performance IQ, Denmark 2003-2008.

	Crude			Adjusted[2]	
Average number of drinks per week before pregnancy	**Mean score**	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Full scale IQ					
0	105.88	Reference	-	Reference	-
15-21	106.84	0.97	[−2.83; 4.76]	2.05	[−3.40; 7.50]
≥22	99.31	−6.57	[−13.36; 0.12]	−6.33	[−12.56; −0.10]
p-value[3]	*0.08*			*0.02*	
Verbal IQ					
0	103.59	Reference	-	Reference	-
15-21	106.04	2.45	[−0.74; 5. 46]	1.99	[−2.78; 6.76]
≥ 22	99.98	−3.61	[−8.35; 1.14]	−4.63	[−9.79; 0.53]
p-value[3]	*0.04*			*0.01*	
Performance IQ					
0	106.84	Reference	-	Reference	-
15-21	105.96	−0.89	[−5.98; 4.20]	1.89	[−5.44; 9.21]
≥22	98.56	−8.29	[−17.88; 1.31]	−6.52	[−16.00; 2.96]
p-value[3]	*0.27*			*0.21*	

[1] Wechsler Preschool and Primary Scale of Intelligence-Revised.

[2] Parental education, maternal IQ, prenatal maternal smoking, child's age at testing, child's sex, and average weekly alcohol intake during pregnancy.

[3] *P*-value for the hypothesis of no difference in IQ-scores across levels of average weekly alcohol intake before pregnancy.

Table 4

Associations between maternal alcohol intake before pregnancy and offspring mean TEACh-5[1], Denmark 2003-2008.

	Crude			Adjusted[2]	
Average number of drinks per week before pregnancy	**Mean score**	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Overall attention					
0	0.00	Reference	-	Reference	-
15-21	0.12	0.11	[−0.23; 0.45]	−0.15	[−0.65; 0.34]
≥22	−0.40	−0.40	[−0.94; 0.13]	−0.80	[−1.35; −0.25]
p-value[3]	*0.18*			*0.01*	
Selective attention					
0	−0.07	Reference	-	Reference	-
15-21	0.06	0.12	[−0.24; 0.48]	−0.13	[−0.62; 0.36]
≥22	0.02	0.09	[−0.32; 0.51]	−0.28	[−0.79; 0.24]
p-value[3]	*0.78*			*0.57*	
Sustained attention					
0	0.07	Reference	-	Reference	-
15-21	0.13	0.06	[−0.26; 0.38]	−0.12	[−0.65; 0.42]
≥22	−0.64	−0.70	[−1.33; −0.08]	−0.97	[−1.66; −0.28]
p-value[3]	*0.06*			*0.01*	

[1] Test of Everyday Attention for Children at Five.

[2] Parental education, maternal IQ, prenatal maternal smoking, child's age at testing, child's sex, and average weekly alcohol intake during pregnancy.

[3] *P*-value for the hypothesis of no difference in IQ-scores across levels of average weekly alcohol intake before pregnancy.

Table 5

Associations between maternal alcohol intake before pregnancy and offspring mean BRIEF[1] index score: the Behavioural Regulation Index (BRI) and the Metacognition Index (MI), Denmark 2003-2008.

	Crude			Adjusted[2]	
Average number of drinks per week before pregnancy	**Mean score**	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
Parent-rated BRI					
0	49.67	Reference	-	Reference	-
15-21	50.70	1.03	[−1.77; 3.83]	2.28	[−2.49; 7.05]
≥22	49.55	−0.12	[−4.43; 4.19]	0.72	[−4.23; 5.68]
p-value [3]	*0.73*			*0.61*	
Parent-rated MI					
0	49.23	Reference	-	Reference	-
15-21	50.95	1.72	[−0.95; 4.39]	3.35	[−1.38; 8.08]
≥22	50.40	1.17	[−2.90; 5.23]	2.21	[−2.92; 7.33]
p-value [3]	*0.44*			*0.37*	
Teacher-rated BRI					
0	49.78	Reference	-	Reference	-
15-21	50.11	0.33	[−2.41; 3.06]	−3.17	[−7.37; 1.02]
≥22	50.34	0.56	[−3.91; 5.03]	−2.15	[−7.35; 3.05]
p-value [3]	*0.96*			*0.36*	
Teacher-rated MI					
0	50.65	Reference	-	Reference	-
15-21	49.63	−1.03	[−3.84; 1.79]	−4.25	[−8.64; 0.14]
≥22	50.30	−0.35	[−4.82; 4.11]	−3.18	[−8.67; 2.32]
p-value [3]	*0.78*			*0.17*	

[1] Behaviour Rating Inventory of Executive Function.

[2] Parental education, maternal IQ, prenatal maternal smoking, child's age at testing, child's sex, and average weekly alcohol intake during pregnancy.

[3] *P*-value for the hypothesis of no difference in IQ-scores across levels of average weekly alcohol intake before pregnancy.

Table 6

Associations between maternal alcohol intake before pregnancy and offspring mean MABC[1] score, Denmark 2003-2008.

	Crude			Adjusted[2]	
Average number of drinks per week before pregnancy	**Mean score**	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
0	7.24	Reference	-	Reference	-
15-21	8.38	1.14	[−1.76; 4.05]	−3.15	[−8.10; 1.80]
≥22	12.12	4.88	[−0.48; 10.24]	2.96	[−1.00; 6.92]
p-value[3]	*0.19*			*0.01*	

[1] Movement ABC.

[2] Parental education, maternal IQ, prenatal maternal smoking, child's age at testing, child's sex, and average weekly alcohol intake during pregnancy.

[3] *P*-value for the hypothesis of no difference in IQ-scores across levels of average weekly alcohol intake before pregnancy.